High-field (500 MHz) ^{1}H NMR Spectra of Retinoic Acids and Arotinoids by Two-dimensional Chemical Shift Correlation (2D) Spectroscopy

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^{1}H NMR Spectra, Retinoic Acids, Arotinoids

The ^{1}H NMR spectra (in DMSO solution at 300 K) of retinoic acids (*cis*- and *trans*-isomers) and new arotinoids were run at 500 MHz and assigned by using homo- and heteronuclear two-dimensional (2D) chemical shift correlation experiments. Spectral analysis was indicating, on the basis of *J* values, that the ring C(1)–C(2)–C(3)–C(4)–C(5)–C(6) adopts, in all compounds, a chair conformation.

Introduction

The human therapeutic usefulness of arotinoids, a new class of highly active retinoids [1, 2], has been proved by positive clinical results in oncology and dermatology [3, 4].

Preliminary to extensive studies of conformational dynamics by NMR methods, we report here the ^{1}H NMR parameters obtained for retinoic acids **1, 2** (vitamin A and its 13-*cis* isomer) and arotinoids **3–7** in the same solvent (DMSO), using homonuclear shift spectroscopy. No data were available for arotinoids, while isomeric vitamins A were included in previous ^{1}H and ^{13}C NMR studies [5, 6] (in $CDCl_3$ solution) of carotenoids and related compounds.

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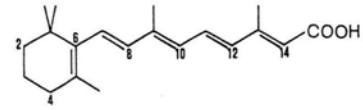
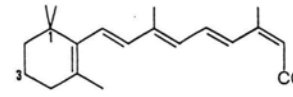
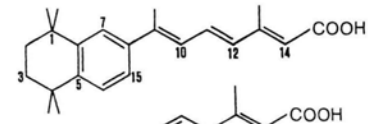
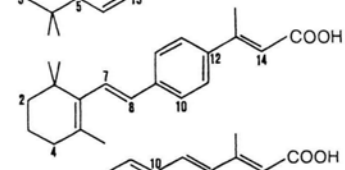
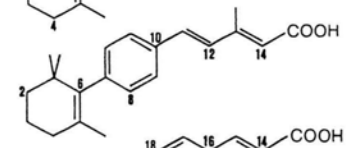
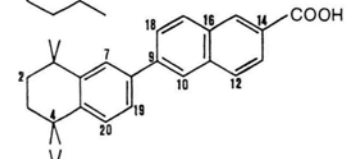
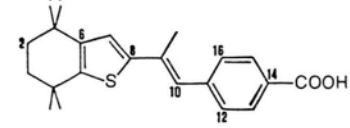
Experimental

^{1}H NMR experiments were performed on a Bruker WM 500 spectrometer operating at 500.13 MHz in the Fourier transform mode. The instrument was equipped with an Aspect 3000 computer, pulse programmer and array processor. The field frequency lock was provided by the deuterium signal of the solvent. All spectra were run at 300 K using 20 mM solutions in dimethylsulfoxide-d_6 (DMSO) CEA, France, in 5 mm tubes. A trace of TMS was added to each solution as internal standard.

The pulse length corresponding to 90° flip angle was 12 μsec. Quadrature detection was used and 16 scans were ω added for normal one-dimensional spectra.

Assignment of resonances was made using two-dimensional (2D) shift correlation (COSY) experi-

Table I. Chemical structure of the compounds **1–7.**

Compound No.	Chemical structure and numbering scheme of atoms
1	
2	
3	
4	
5	
6	
7	

ments [7], using 256 time increments. The final matrix was 1K×1K in size. Sine bell windows were used as apodization functions in both dimensions and all data were obtained in the absolute value mode. Based on previous ^{13}C NMR studies in $CDCl_3$ [5], further check of assignments for **1** and **2** was achieved using classical [8], long-range (COLOC) [9] and relayed [10] heteronuclear ($^{13}C-^{1}H$) correlation experiments.

The ^{13}C NMR spectra of **1** and **2** were run at 75.47 MHz on a Bruker MSL 300 spectrometer at 300 K using saturated solutions (in DMSO) in 10 mm tubes (256 scans, proton decoupling by broad band modulation).

Heteronuclear shift correlation spectra were run using 256 time increments; the final matrix was 1K×1K in size. Internal TMS was the reference in both dimensions. Processing of the 2D experiments was the same as that used for ^{1}H spectra. Under our experimental conditions, the 90° pulses were 8 μsec and 18 μsec in length for ^{13}C and ^{1}H (decoupler channel), respectively. Correlation maps are shown in Fig. 1.

Molecular formulas and numbering scheme of atoms of compounds **1–7** are shown in the Table I.

Synthesis and characterization of the samples are reported elsewhere [1, 2].

Discussion

The spectral parameters are collected in Table II.

The coupling constant values for nuclei in the 2-, 3-, 4-positions were not attainable because the computerized fitting procedure, performed by using the PANIC programme (Bruker version of the LAOCOON III programme [11]), for the experimental

Table II. ^{1}H NMR Spectral parameters for retinoids and arotinoids **1–7** measured at 500 MHz in DMSO solution (300 K).

Chemical shifts (δ)	**1**	**2**	**3**	**4**	**5**	**6**	**7**
Me(1)	1.01	1.01	1.23*	1.04	0.88*	1.27*	1.19
Me(4)			1.27*			1.33*	1.26
Me(5)	1.68	1.68		1.73	1.23*		
Me(9)	1.97	1.98	2.21				2.24
Me(13)	2.27	2.03	2.30	2.48	2.32		
H(2)	1.43	1.43	1.63	1.45	1.53	1.67	1.62*
H(3)	1.57	1.57	1.63	1.59	1.67	1.67	1.66*
H(4)	2.00	2.00		2.02	2.01		
H(7)	6.25	6.24	7.43	6.79		7.73	7.11
H(8)	6.15	6.21		6.38	6.95		
H(9)					7.53		
H(10)	6.22	6.27	6.65	7.50		8.25	6.88
H(11)	7.02	7.01	7.06	7.50	7.02		
H(12)	6.39	7.69	6.53		7.02	7.91	7.46
H(13)						8.17	7.92
H(14)	5.76	5.62	5.80	6.12	5.94		
H(15)			7.27	7.50	7.53	8.62	7.92
H(16)			7.29	7.50	6.95		7.46
H(17)						8.00	
H(18)						8.07	
H(19)						7.55	
H(20)						7.43	

* These assignments can be inverted.

upling constants (Hz)	**2**	**3**	**4**	**5**	**6**	**7**
, 8) = 16.2	*J*(7, 8) = 16.0	*J*(7, 16) = 0.5	*J*(7, 8) = 15.6	*J*(8, 9) = 8.4	*J*(7, 19) = 2.0	*J*(10, Me-9) = 1.3
, Me-5) = 0.5	*J*(7, Me-5) = 0.5	*J*(7, 15) = 1.8	*J*(7, Me-5) = 0.8	*J*(8, 15) = 0.8	*J*(10, 12) = 1.8	*J*(12, 13) = 6.5
0, 11) = 12.7	*J*(10, 11) = 12.9	*J*(10, 11) = 11.2	*J*(10, 11) = 8.9	*J*(8, 16) = 1.9	*J*(10, 18) = 1.2	*J*(12, 16) = 1.9
0, Me-9) = 1.0	*J*(10, Me-9) = 1.0	*J*(10, Me-9) = 1.3	*J*(10, 14) = 1.9	*J*(9, 15) = 1.9	*J*(12, 13) = 8.6	*J*(13, 15) = 1.9
1, 12) = 15.3	*J*(11, 12) = 15.3	*J*(11, 12) = 15.1	*J*(11, 13) = 1.9	*J*(9, 16) = 0.8	*J*(13, 15) = 1.0	*J*(15, 16) = 6.5
4, Me-13) = 1.3	*J*(14, Me-13) = 0.8	*J*(14, Me-13) = 1.3	*J*(14, Me-13) = 1.3	*J*(11, 12) = 15.3	*J*(15, 17) = 1.7	
		J(15, 16) = 8.3	*J*(15, 16) = 8.9	*J*(14, Me-13) = 1.2	*J*(19, 20) = 8.2	

patterns arising from H-2,2′, H-3,3′, H-4,4′ (compounds **1, 2, 4, 5**) and from H-2,2′, H-3,3′ (compounds **3, 6, 7**) spin-systems, failed. The iterative analysis and refinement of the spectral parameters was impossible because of the small number of resolved lines.

In the first trial simulation of the spectra, which was made with chemical shifts values measured on the spectra at the center of the pertinent multiplets, in all cases the use of sets of J's compatible with a more or less distorted chair conformation of the ring, produced theoretical patterns in acceptable agreement with the experimental ones, although not suited for iteration due to the lack of resolution.

Trial parameters that were deduced for a boat conformation of the hexatomic ring gave simulated spectra (Lorentzian line shapes) markedly different from the experimental patterns.

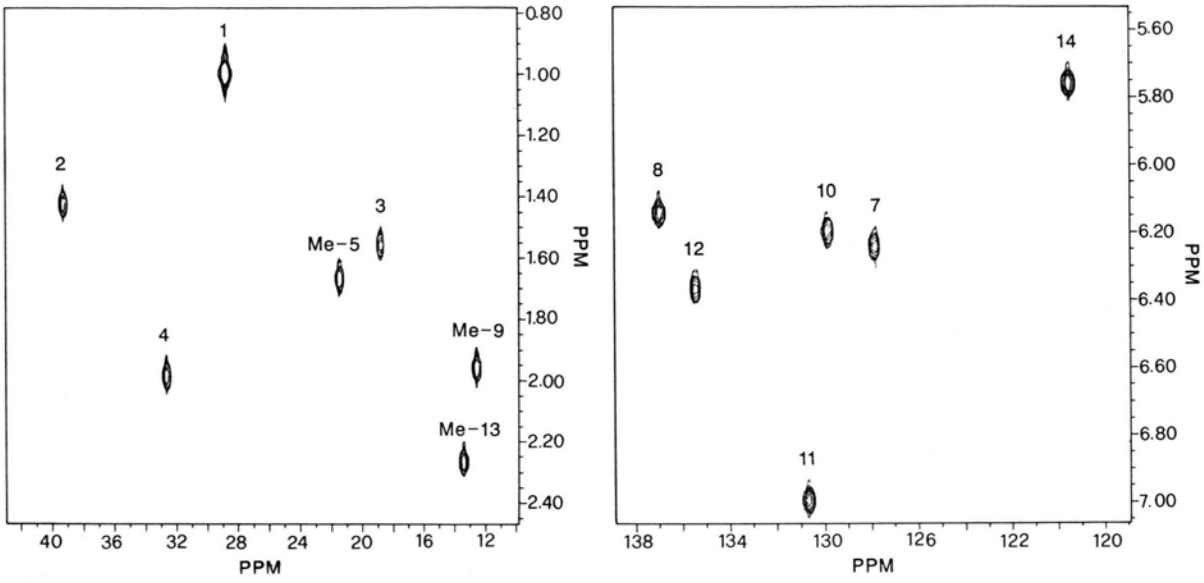


Fig. 1. The $^{13}C-^{1}H$ shift correlation of **1** in DMSO solution.

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